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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/577,657	05/25/2000	Misako Mizuno	029430-454	6902

21839 7590 02/17/2004

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EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/577,657	MIZUNO ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *29-31,33-36 and 38-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-31, 33-36 and 38-53* is/are rejected.

7)☒ Claim(s) *54 and 55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 November 2003 has been entered.

2. Claims 29-31, 33-36 and 38-55 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

4. Claim 51 remains objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Parent claim 49 already specifies that the plant is Camellia or Coffee. The objection is repeated for the reasons of record as set forth in the Office action mailed 21 May 2003. Applicant's arguments filed 21 November 2003 have been fully considered but they are not persuasive.

Applicant urges that the claim limits the parent claim to plants, excluding plant cells and plant tissues (response pg 12).

This is not found persuasive because the claim merely states that the transformed whole plant is cultured Camelia or Coffea, which the parent claim also recites. If Applicant wishes to

limit the method to a whole plant, the claim should be amended to replace "said transformed ... Coffea plant" with --a transformed whole plant is cultured--.

5. Claims 54-55 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

6. Claims 29-34 are objected to because there is an improper article before "N-methyl" in line 2.

Claim Rejections - 35 USC § 112

7. Claims 29-31, 34-36 and 39-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids of SEQ ID NO:2 and plant cells and plants transformed with those nucleic acids, does not reasonably provide enablement for nucleic acids that encode SEQ ID NO:1 or nucleic acids that have 90% identity to any nucleic acid that encodes SEQ ID NO:1 or for RNA vectors and plants transformed therewith. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the Office action mailed 21 May 2003, as applied to claims 29-32, 34-37, 39-49 and 52-53. Applicant's arguments filed 21 November 2003 have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids encoding SEQ ID NO:1 or nucleic acids that have 90% identity to any nucleic acid that encodes SEQ ID NO:1 and that encodes an enzyme that is an N3-methyl transferase, a theobromine N1 methyl transferase and a

paraxanthine N3 methyl transferase, vectors comprising the nucleic acids, any plant cell or plant comprising the vectors, a method of producing a plant secondary metabolite and a method of modifying the concentration of caffeine in a *Coffea* or *Camellia* plant.

The instant specification, however, only provides guidance for isolation of N methyl transferase from *Camellia sinensis* var. *Yabukita* (example 1); amino acid sequencing of the N-terminal portion of the enzyme to produce SEQ ID NO:4 (example 2); use of a primer based on that sequence as a probe against a cDNA library from an unspecified source to isolate SEQ ID NO:5 (example 4); use of RT-PCR to isolate the coding sequence (SEQ ID NO:3, which encodes SEQ ID NO:1) from a tea cDNA library (examples 4-7); 5'-RACE to isolate the 5' upstream region to produce a gene sequence of SEQ ID NO:2 (example 8); expression of the enzyme in *E. coli* and testing of enzyme activities to show that the enzyme has the activities of an N3-methyl transferase, a theobromine N1 methyl transferase and a paraxanthine N3 methyl transferase (example 9); and antisense suppression of caffeine synthesis in coffee (example 10).

The instant specification fails to provide guidance for nucleic acids that have 90% identity to any nucleic acid that encodes SEQ ID NO:1 and that encode an enzyme that is an N3-methyl transferase, a theobromine N1 methyl transferase and a paraxanthine N3 methyl transferase, vectors comprising the nucleic acids, plant cells or plants comprising the vectors, a method of producing a plant secondary metabolite and a method of modifying the concentration of caffeine in a *Coffea* or *Camellia* plant

The specification fails to provide guidance for which amino acids are critical for protein function and which are not and can thus be altered. One method, making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another)

does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). The nucleic acids encoding all these mutated proteins, however, would hybridize under very high stringency to the nucleic acids encoding the original protein.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids encoding proteins with N3-methyl transferase, theobromine N1 methyl transferase and paraxanthine N3 methyl transferase activities. Making all possible single amino acid substitutions in a 356 amino acid long protein like that encoded by SEQ ID NO:2 would require making and analyzing 19^{356} nucleic acids. Nucleic acids with 90% identity to the portion of SEQ ID NO:2 that encodes SEQ ID NO:1 would be at least 1068 nucleotides long and would have up to 106 nucleotides substitutions compared to that portion of SEQ ID NO:2; this would mean that the proteins encoded by these nucleic acids could encode a protein with 106 amino acid substitutions compared to SEQ ID NO:1; these proteins would have only 70.2% identity to SEQ ID NO:1. The specification does not teach nucleic acids that encodes proteins with N3-methyl transferase, theobromine N1 methyl transferase and paraxanthine N3 methyl transferase

activities and that have 70.2% identity to SEQ ID NO:1. Nucleic acids with 90% identity to any nucleic acid that encodes SEQ ID NO:1 would encode proteins even more amino acid substitutions compared to SEQ ID NO:1, and the specification does not teach any of these nucleic acids. As the specification does not provide guidance for these nucleic acids, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims, if such nucleic acids are even obtainable.

As discussed in the prior Office actions, SEQ ID NO:1 is not the entire protein sequence. Kato et al (2000, Nature 406:956-957) teach a gene encoding a caffeine synthase that is identical to the caffeine synthase of the instant invention except the published enzyme is 13 amino acids longer at its N-terminal (see sequence search results sent with the Office action of 16 October 2001). All experiments involving transformation used a DNA comprising SEQ ID NO:2, which is almost identical to the nucleic acid taught by Kato et al and would encode the full-length enzyme. There is no evidence to suggest that a nucleic acid encoding only SEQ ID NO:1 would function to encode an enzyme with the listed properties, especially since the starting methionine is missing.

Claims 45-48 are drawn to any plant transformed with the claimed nucleic acid. However, few plant species would have the enzyme required to produce the substrate for the enzyme of SEQ ID NO:1 and few would have an nucleic acid whose expression could be silenced by a nucleic acid encoding SEQ ID NO:1. Thus, it is not clear how one would use any plant transformed with a nucleic acid encoding SEQ ID NO:1.

Furthermore, neither the specification nor the prior art teaches how to transform any member of the *Coffea* or *Camellia* genera. *Coffea* includes *C. abeokutae, C. arabica, C.*

arnoldiana, C. aruwimiensis, C. bertrandi, C. brevipes, C. canephora, C. congensis, C. costatifructa, C. dolichophylla, C. eugenioides, C. excelsa, C. farafanganensis, C. humblotiana, C. humilis, C. kapakata, C. khasiana, C. liberica, C. millotii, C. perrieri, C. pseudozanguebariae, C. racemosa, C. resinosa, C. sakarahae, C. salvatrix, C. sessiliflora, C. stenophylla, and *C. zanguebariae*, while *Camellia* includes *C. achrysantha, C. albogigas, C. chrysanthoides, C. fascicularis, C. flavida, C. fusuiensis, C. grandis, C. granthamiana, C. grijsii, C. henryana, C. huana, C. impressinervis, C. japonica, C. lanceolata, C. liberofilamenta, C. limonia, C. longgangensis, C. longruiensis, C. longzhouensis, C. micrantha, C. multipetala, C. nitidissima, C. parvipetala, C. petelotii, C. pingguoensis, C. ptilosperma, C. pubipetala, C. salicifolia, C. sasanqua, C. sinensis, C. terminalis, C. tunghinensis, C. xiashiensis,* and *C. yunnanensis.* Transformation of only a few of these species is possible.

As the specification does not describe the isolation of any nucleic acid other than SEQ ID NOs:2-3 or the transformation of any plant with any nucleic acid other than SEQ ID NO:2, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those nucleic acids that encode proteins with N3-methyl transferase, theobromine N1 methyl transferase and paraxanthine N3 methyl transferase activities, if such enzymes are even obtainable and those plants with altered concentrations of caffeine, xanthine, paraxanthine or theobromine, if such plants are even obtainable.

Applicant urges that it is within the abilities of the skilled artisan to make and use the claimed nucleic acids based on SEQ ID NOs:1 and2 (response pg 13).

This is not found persuasive because the specification does not teach any nucleic acid that has 90% identity to any nucleic acid that encodes SEQ ID NO:1, nor does it teach which amino acids to modify and which amino acids are critical to enzymatic function to provide guidance for making the claimed nucleic acids.

Applicant urges that in bacteria, GUG and UUG also act as start codons and in SEQ ID NO:2, immediately preceding the amino acid of SEQ ID NO:1, GTG is present, at nucleotides 93-95, and this GTG can act as a start codon in bacteria. Applicant also urges that one can use SEQ ID NO:1 by adding a start codon to it because SEQ ID NO:2 teaches one to do so and because the claims "comprise" SEQ ID NO:1 (response pg 12).

This is not found persuasive. First, the claims are drawn to nucleic acids encoding SEQ ID NO:1, and thus nucleic acids encoding only SEQ ID NO:1, which lacks an ATG, GTG or TTG start codon, must be useable. Second claims 45-48 are drawn to a plant transformed with a nucleic acid encoding SEQ ID NO:1, and GUG and UUG start codons do not work in plants. Third, inferring that SEQ ID NO:2 teaches one to use a GTG start codon is a stretch, especially since that codon is located several codons before the point at which SEQ ID NO:1 starts.

8. Claims 29-31, 34-36 and 39-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 21 May 2003, as applied to claims 30, 32, 35, 37, 40, 42, 44, 46, 48 and 53. Applicant's arguments filed 21 November 2003 have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of nucleic acids that have 90% identity to any nucleic acid that encodes SEQ ID NO:1. In contrast, the specification only describes a coding sequence from *Camellia sinensis* that comprises SEQ ID NO:2. Applicant does not describe other nucleic acids encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described nucleic acids that have 90% identity to any nucleic acid that encodes SEQ ID NO:1 within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

Applicant urges that having knowledge of the amino acid sequence of SEQ ID NO:1, one of skill in the art could readily create and modify sequences with 90% identity thereto and determine if the maintain the required enzyme activities (response pg 14).

This is not found persuasive because the specification does not teach the structural features, *i.e.*, the sequence, of a single nucleic acid that has 90% identity to any nucleic acid that encodes SEQ ID NO:1 and that encodes a protein with N3-methyl transferase, theobromine N1 methyl transferase and paraxanthine N3 methyl transferase activities. The critical structural motifs that distinguish nucleic acids that encode functional enzymes from those that do not are not described.

9. Claims 30-31, 35-36, 40, 42, 44, 46, 48-49, 51 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is modified from the rejection set forth in the Office action mailed 21 May 2003, as applied to claims 30-33, 35-38, 40, 42, 44, 46, 48, 51 and 53. Applicant's arguments filed 21 November 2003 have been fully considered but they are not persuasive.

Claim 30 lacks antecedent basis for the limitation "the nucleotide sequence of claim 29" as claim 29 is drawn to a DNA molecule.

Claim 35 lacks antecedent basis for the limitation "the nucleotide sequence of claim 34" as claim 34 is drawn to an RNA molecule.

Applicant urges that claims 29 and 34 claim DNA and RNA molecules, respectively, that comprise nucleotide sequences; thus there is sufficient antecedent basis for "the nucleotide sequence of" in claims 30 and 35 (response pg 14-15).

This is not found persuasive. There would be antecedent basis for "the nucleotide sequence encoding an N-methyl transferase of SEQ ID NO:1", but as claims 29 and 34 are drawn to DNA and RNA molecules, respectively, there is no antecedent basis for "the nucleotide sequence of claim 29" and "the nucleotide sequence of claim 34".

The following rejections are new:

Claim 49 lacks antecedent basis for the limitation "said transformed plant cell, plant tissue, or whole plant" in lines 4 and 3, respectively.

Claim 49, lines 5 and 6, and claim 50, lines 4 and 5, are indefinite in their recitation of "plant body". The specification defines "plant body" as "the whole individual organism classified into plant or organ parts thereof such as leaves, stems, roots, flowers, fruits, seeds and

the likes" [sic]. Culturing a whole plant to form a plant body would therefore mean culturing a whole plant to form a whole individual plant; the phrase is redundant and meaningless.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
February 3, 2004